Refer to: Roberts JM: Preeclampsia and eclampsia—Medical Staff Conference, University of California, San Francisco. West J Med 135:34-43, Jul 1981

Preeclampsia and Eclampsia

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr, Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR. NAUGHTON:* *The topic of this Medical Grand Rounds is preeclampsia and eclampsia. Dr. Rhyner will begin the discussion by presenting a case.*

DR. RHYNER:† The patient is a 23-year-old woman (gravida 2, para 0, abortus 1) who at 36 weeks of pregnancy went to her physician because of increasingly severe headaches and visual blurring for two or three days. Her pregnancy had been uncomplicated, and she had no history of hypertension. During the examination she had a grand mal seizure. Findings of an initial evaluation included a blood pressure of 120/90 mm of mercury and proteinuria (3+). Treatment with magnesium sulfate was begun and she was transferred to this hospital. On admittance to the Obstetrics Service, the patient was awake and alert. Her blood pressure was 140/90 mm of mercury, with a heart rate of 90 beats per minute. Her fundi were benign and there was no thyromegaly. Her lungs were clear and there were no cardiac gallops or murmurs. Neurological examination showed that her reflexes were 4+ with bilateral clonus.

Laboratory data on admission included 13 grams of hemoglobin per dl, a hematocrit of 38.1 percent and 194,000 platelets per cu mm. Prothrombin time was normal at 11.2 seconds; fibrinogen was 293 mg per dl and fibrin-split products were 100 mg per dl. SMA-6 showed sodium 138, potassium 3.6, chloride 102 and bicarbonate 22 mEq per liter. Blood urea nitrogen was 12 and creatinine 1.1 mg per dl.

During the hospital course the patient underwent oxytocin- (Pitocin-) induced labor and gave birth to a 2,300 gram girl, with Apgar scores of 8 and 9. Magnesium sulfate therapy was continued for 24 hours and phenobarbital was added. Her blood pressure remained 130/80 mm of mercury and her reflexes were normal. Forty-eight hours after delivery she was noted to have tachycardia with a rate of 130 per minute. At this time, her blood pressure was 170/100 mm of mercury, and she was afebrile. On examination of her chest, left lower lobe rales were noted; results of an x-ray study of the chest showed a left lower lobe infiltrate and a small effusion. Blood gases while breathing room air showed a pH of 7.49, oxygen pressure (Po_2) of 42 and carbon dioxide pressure (Pco_2) of 34 mm of mercury. Bilateral rales and a gallop rhythm rapidly developed and repeat x-ray films of the chest showed the development of large bilateral pleural effusions and pulmonary edema. Findings of a lung scan were negative. The pleural fluid was a transudate. Tests for anti-double-stranded DNA antibody, fibrin-split products and fibrinogen were negative. She was transferred to the coronary care unit where hemodynamic monitoring showed a right atrial pressure

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of 8, a pulmonary capillary wedge of 28 and pulmonary artery pressure of 35/20 mm of mercury; her cardiac output was 5.3 liters per minute. Cardiac function was within normal range, based on results of an echocardiogram. She was treated with supplemental oxygen, nitroprusside, furosemide (Lasix) and propranolol. At discharge, her blood pressure was 120/70 mm of mercury, her gallop rhythm had resolved and blood gases while breathing room air showed a pH of 7.39, Po_2 of 81 and a Pco_2 of 43 mm of mercury.

DR. NAUGHTON: *Next, Dr. James Roberts of the Department of Obstetrics and Gynecology will discuss preeclampsia-eclampsia from a perspective relevant to nonobstretricians.*

DR. ROBERTS:* The patient described above manifested a challenging and fascinating clinical problem, preeclampsia-eclampsia. The disease is challenging because it tests both the medical and obstetrical skills of the clinicians involved. Our medical skills are tested by the derangements of many physiological processes. For example, in our patient there was evidence of a central nervous system abnormality manifested by convulsions, and changes in renal function indicated by a serum creatinine concentration of 1.1 mg per dl (decidedly elevated for a woman in late pregnancy). In addition, there was evidence of disseminated intravenous coagulation with elevated fibrin-split products and decreased platelets and fibrinogen, compared with normal values during pregnancy. If liver function had been tested, I am sure that it would have been found to be abnormal as well. The most significant physiological derangement for this woman was pulmonary edema, a condition that is not seen frequently in women with preeclampsia-eclampsia. The incidence of pulmonary edema is probably less than 10 percent. This is fortunate because the mortality rate reported for eclampsia complicated by pulmonary edema is high.[1]

Hemodynamic changes in women with eclampsia and pulmonary edema have not been studied extensively. In the few women in whom such changes were documented, the changes were similar to those in our patient. In other patients relatively normal indexes were noted when Swan-Ganz catheters were inserted.[2] The cause of this condition has not been determined. One possible explanation is that normally there is a massive mobilization of interstitial fluid 24 to 48 hours postpartum in women with preeclampsia. This usually results in a dramatic diuresis; however, occasionally the increased intravascular volume is not tolerated and results in pulmonary edema. In some cases, the fluid mobilization is not tolerated because the patient has substantial oliguria due to renal effects of preeclampsia. In patients with pulmonary edema that I have seen previously, this has been the usual inciting factor. In our patient it is difficult to determine whether renal problems or an intrinsic cardiac defect accounted for inability to tolerate this fluid shift or whether the congestive heart failure was in some way related to the profound vasospasm present in eclampsia. However, it is obvious that the use of hemodynamic monitoring and an appropriate approach to management resulted in a benign course. I suspect that the reported high mortality of pulmonary edema related to eclampsia would be less if the above approaches were attempted.

Another interesting point in this case is the fact that the patient's blood pressure was not exceptionally elevated—the highest diastolic pressure recorded was 100 mm of mercury—in spite of the fact that she manifested many physiological derangements. This is an important feature of preeclampsia, which I will discuss in some detail.

Preeclampsia-eclampsia is challenging to obstetricians. Attempts to palliate the mother's medical condition with the baby *in utero* must be done with the knowledge that treatment may compromise the fetus, either directly or, more important, by effects on uterine blood flow. Once a woman is eclamptic, delivery is almost always an appropriate management. Another obstetrical challenge in the management of patients seeking medical attention at earlier stages of this disease is to determine whether the fetus, which is at increased risk, is safer remaining *in utero* or being delivered; certainly in this woman there was no question. Obstetricians are faced with a critical decision in determining whether to induce delivery of the fetus.

I mentioned above the fascinating nature of preeclampsia-eclampsia. At least part of this is because no clear-cut cause has been determined other than the fact that the women with the disorder are pregnant. It is also intriguing that the impressive derangements of physiological function that occur all return to normal with the termination of pregnancy.

Over the years varying forms of nomenclature

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TABLE 1.—*Hypertensive Disorders in Pregnancy*

Chronic hypertensive disease
Blood pressure >140/90 mm of mercury before 20 weeks of gestation
Preeclampsia-eclampsia
Blood pressure elevation >15 mm of mercury diastolic or 30 mm of mercury systolic
Proteinuria >0.3 gram/24 hours
Edema

have been used to differentiate women who are already hypertensive and then become pregnant from those who have preeclampsia-eclampsia (Table 1). It is assumed that if a woman has an elevated blood pressure of greater than 140/90 mm of mercury before 20 weeks gestation, she was hypertensive before pregnancy. This aspect of the diagnosis is becoming easier to confirm because today many women know their blood pressure before they become pregnant. Preeclampsia-eclampsia is characterized not by a fixed elevated blood pressure but by blood pressure increases, 15 mm of mercury diastolic or 30 mm of mercury systolic, over values recorded in early pregnancy.[3] It is likely that this occurred in our patient because most young women in early pregnancy will have blood pressures in the range of 110/60.

In addition to blood pressure elevation, patients with preeclampsia-eclampsia frequently have proteinuria, which is defined as the excretion of more than 0.3 gram of protein per 24 hours, and sodium retention that leads to edema. The disease primarily involves women in their first pregnancy —two thirds of all cases occur within this group. There is a wide range in the severity of the disease. Some cases just barely satisfy diagnostic criteria of blood pressure, proteinuria or edema (or a combination of two of these); others involve more substantial blood pressure elevation and proteinuria, and, finally, the most serious cases involve seizures as well.

The diagnosis of preeclampsia is based on the presence of at least two of the three criteria—elevated blood pressure, edema and proteinuria. Eclampsia is preeclampsia plus convulsions. It is important to realize that women do not become eclamptic de novo but rather progress from being mildly preeclamptic to more severely preeclamptic to eclamptic. Because the vast majority of patients with mild-to-moderate eclampsia are asymptomatic, attempts to recognize mild preeclampsia before it progresses to eclampsia necessitate frequent obstetrical visits in late pregnancy. This progression can occur slowly over time such that the mild preeclampsia develops and the woman's condition changes minimally over the remainder of her pregnancy. Or, it may progress quickly so that the woman is mildly preeclamptic at 34 weeks of gestation and severely preeclamptic at 38 weeks or, in the most frightening of cases, the spectrum can be traversed rapidly—in a matter of days. Obstetrical management in late pregnancy should be directed at trying to identify women who are preeclamptic in order to recognize any patient whose condition is rapidly worsening.

I will now discuss the pathological and pathophysiological changes that occur[3] and the philosophy of obstetric management, especially the question of the short-term and long-term prognoses of the mother and baby. I will also discuss the rationale for the pharmacological agents that are used in the management of severely preeclamptic women and the necessity of follow-up.

Preeclampsia is not just elevated blood pressure or an unmasking of essential hypertension. It is a disease with manifestations that are very different than those in women who are hypertensive before pregnancy. Most obstetricians who deal with preeclampsia feel that from a clinical point of view, blood pressure elevation alone is not the most important pathophysiological factor. Frequently, as in our patient's case, women with preeclampsia will have multisystem disease with blood pressure measurements that are not at a level usually associated with any symptoms. This impression from clinical observation is supported by pathological changes that occur in women who die of eclampsia.[3] The common denominator is that the changes seem not to involve blood vessel disruption but rather are changes associated with poor tissue perfusion, such as periportal hepatic necrosis and hemorrhage and necrosis in the heart and adrenal glands. Even though cerebral hemorrhage is common, massive cerebral hemorrhage occurs in only 10 percent to 15 percent of women dying of eclampsia. Most patients have intracranial petechial hemorrhages, which are usually associated with asphyxia or poor perfusion.

In preeclampsia-eclampsia there is decreased perfusion to a number of vital organs, including the liver, kidney, brain and, very importantly, the uterus and choriodecidual space (Table 2). The last change is of prime importance because fetal well-being may be substantially compromised. Evaluating other cardiovascular variables (Table

TABLE 2.—*Regional Blood Flow Changes in Normal Pregnancy and in Preeclampsia-Eclampsia*

	Normal Pregnancy vs. Nonpregnancy	*Preeclampsia-Eclampsia vs. Normal Pregnancy*
Liver	→	↓
Kidney	↑	↓
Cerebral	→	→
Extremity blood flow	→	→
Uterus	↑	↓
Choriodecidual space	..	↓

→ = no change; ↑ = increased; ↓ = decreased.

TABLE 3.—*Cardiovascular Changes in Preeclampsia-Eclampsia*

	Normal Pregnancy vs. Nonpregnancy	*Preeclampsia-Eclampsia vs. Normal Pregnancy*
Plasma volume	↑	↓
Red blood cell volume	↑	↓
Cardiac output	↑	→
Total peripheral resistance	↓	↑

↑ = increased; ↓ = decreased; → = no change.

3) indicates that cardiac output is unchanged. Therefore, the increased blood pressure is due to increased total peripheral resistance, suggesting that the poor perfusion may be the result of vasospasm. Changes of red blood cell mass and plasma volume are similar to those present in persons with end-stage shock and massive vasoconstriction. On the basis of these findings, it is evident that the blood pressure changes that occur in preeclampsia are secondary to a vasospastic process that has as its most important manifestation a decrease in perfusion of a number of vital organs. It does not seem that the elevation of blood pressure per se brings about the damage. There is also a dramatic decrease in the renal glomerular filtration rate in preeclamptic women compared with normal pregnant women. This is an almost universal finding. A large part of the decreased glomerular filtration rate is explained by changes in renal blood flow. The change is not entirely explained by this, however, since the filtration fraction is also decreased. Uric acid clearance is decreased and, thus, hyperuricemia becomes one of the most reliable laboratory tests to differentiate preeclampsia from essential hypertension. Renal tubular function remains relatively normal, but the decreased glomerular filtration rate results in decreased delivery of sodium to tubules that continue to reabsorb sodium at a normal rate. The imbalance between glomerular and tubular function results in sodium retention. This retention does not require the existence of excess of a known or unknown mineralocorticoid. Changes visualized in renal biopsy specimens of preeclamptic patients again emphasize that preeclampsia is not simply essential hypertension[4,5] (Figure 1). The capillary lumen of the glomeruli from kidneys of preeclamptic women is occluded by swollen endothelial cells. The basement membrane contains inclusions but is otherwise relatively normal. The epithelial foot

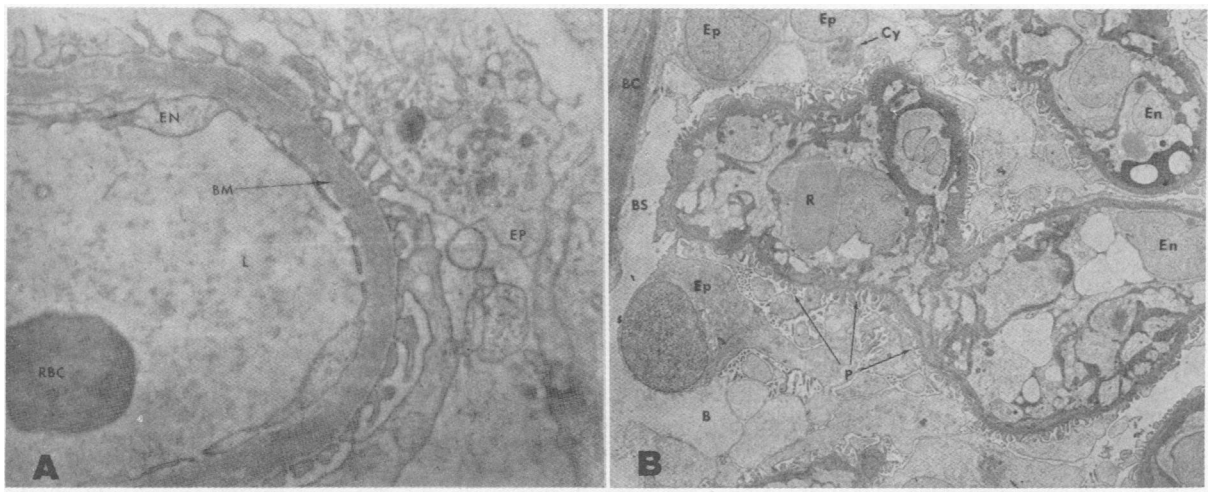

Figure 1.—Electron photomicrographs of renal biopsy specimens from normal **(A)** and preeclamptic **(B)** pregnant women: **A,** Glomerulus of normal pregnant woman. (RBC = red blood cell, EN = endothelial cell, L = capillary lumen, BM = glomerular capillary basement membrane, EP = renal epithelial cell.) (From McCartney.[4]) **B,** Glomerulus of preeclamptic woman. (R = red blood cell [in capillary lumen], En = endothelial cell, Ep = epithelial cells, P = epithelial cell podocytes, Cy = cytoplasmic inclusions.) Note that capillary lumen is virtually occluded by endothelial cells, which are swollen and contain inclusions, but that epithelial foot processes are normal. (From Faith and Trump.[5])

processes also appear to be normal. This finding is termed glomerular endotheliosis and can account for the decreased glomerular filtration that occurs beyond that caused by decreased renal blood flow. On the basis of the information presented, it appears that hypertension and sodium retention are secondary changes rather than primary pathogenic factors in the disease.

There is other recent information regarding the pathogenesis of preeclampsia that explains a number of clinical observations. Women in whom preeclampsia develops very quickly, over 24 to 48 hours, frequently give birth to babies that are severely growth retarded. Therefore, uterine perfusion was decreased long before the disease was clinically evident. Recent studies emphasize that the pathogenic changes antedate the clinical diagnosis of preeclampsia. It has been known for some time that women with preeclampsia are highly sensitive to any pressor agent.[6] They are more sensitive to norepinephrine or vasopressin, but the most impressive difference is seen in responsiveness to angiotensin. When one compares angiotensin responsiveness in normal pregnant women with that in women who are not pregnant, the normal pregnant women are actually less sensitive. Studies from Gant and co-workers[7] showed that the increased sensitivity to angiotensin precedes clinical preeclampsia (Figure 2). Increased sensitivity to angiotensin II is present as early as 14 weeks of gestation, while the clinical diagnosis of preeclampsia is not usually evident until 28 to 30 weeks of gestation. Other evidence for the existence of preeclampsia, before clinical diagnosis, can be obtained by carefully monitoring blood pressure throughout gestation (Figure 3). As early as 17 weeks gestation, the blood pressure measurements of most women who will become preeclamptic are already higher than those of women who will not.[8] Although the difference is statistically significant, the overlap, unfortunately, is too great to allow prediction in a given patient.

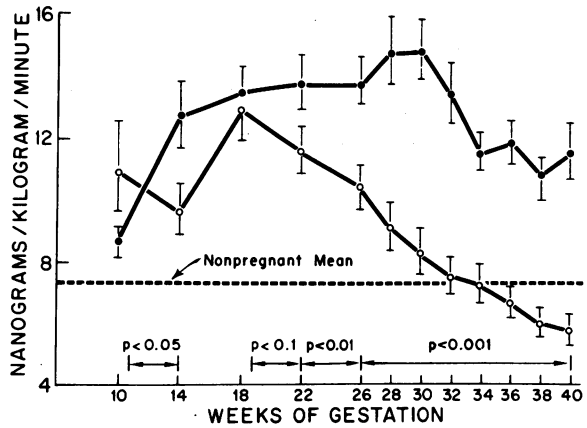

Figure 2.—Angiotensin sensitivity: Comparison of the angiotensin II dose (ng/kg/min) necessary to raise the diastolic pressure 20 mm of mercury in 120 women who remained normotensive (•) and 72 women in whom increased blood pressure developed in late gestation (o). (From Gant et al.[7])

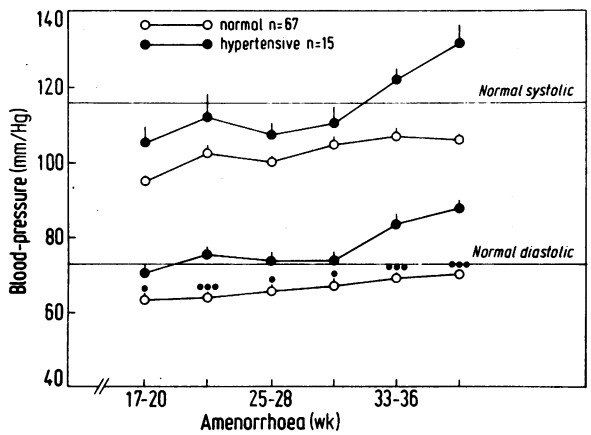

Figure 3.—Blood pressure at different gestational ages: Pregnant women had their blood pressure carefully measured through gestation. Average blood pressure of women in whom elevated blood pressure developed in late gestation (•) are compared with women who remained normotensive (o). Differences were statistically significant as early as 17 weeks gestation (•$P<0.05$; •••$P<0.001$). (From Gallery et al.[8])

We must consider the impact of the disease on mother and baby. Preeclampsia is very rarely associated with maternal mortality. However, if a woman becomes eclamptic, her risk of dying is about 3 percent to 5 percent.[3] Although this percentage does not represent a high mortality rate compared with certain other diseases that one deals with in medical practice, this figure is frightening when we consider that these are young healthy women with a completely reversible disease process. Moreover, the fetus is at increased risk even in a woman with preeclampsia. This infant has about five times the chance of dying as an infant of a mother who does not have this disease. That fivefold increase exists regardless of when in gestation the fetus is delivered.[9] If the woman becomes eclamptic, the perinatal mortality rate increases to approximately 20 percent. Thus, the disease presents a much greater risk of death to the fetus than to the mother.

In making management decisions, we must also consider the long-range outcome for the mother.

The relationship of preeclampsia to the development of hypertension in subsequent years is controversial. Virtually every study that has followed previously preeclamptic women for many years has concluded that the incidence of hypertension is increased in later life.[10,11] It is important to try to determine whether preeclampsia unmasks a hypertensive problem that was already present or whether preeclampsia occurs because the woman has an independent problem that increases the risk of developing both preeclampsia and hypertension in later years. Is it possible that preeclampsia damages kidneys or blood vessels and causes a woman, who would have been normotensive 20 years later, to become hypertensive?

The normal blood pressure changes of pregnancy lead to problems in the diagnosis of preeclampsia and in determining the long-range prognosis of preeclampsia[12] (Figure 4). In early pregnancy both diastolic and systolic blood pressures decrease by about 7 mm of mercury. This is the average; thus, in some women blood pressure will decrease to a greater extent. In our experience, it appears that in women who are hypertensive before pregnancy, blood pressure will decrease by more than 7 mm of mercury. For example, if a woman with undiagnosed hypertension did have a blood pressure decrease of 15 mm of mercury diastolic in early gestation, she would be considered normotensive at this time. When her blood pressure increased to its usual levels in late pregnancy, she would be diagnosed as preeclamptic. When she was seen post partum with her usual elevated blood pressure, it would be judged that her preeclampsia had resulted in persistent hypertension.

This difficulty in diagnosis can be illustrated by examining renal biopsy specimens of preeclamptic women (Table 4). Results of renal biopsies of women with preeclampsia during their first pregnancy indicate that about 70 percent will have glomerular endotheliosis, the lesion I discussed earlier. However, 25 percent of these women will also have evidence of underlying renal disease that was not suspected before the renal biopsy.[4] When renal biopsy specimens from women who have preeclampsia during later pregnancies are examined, very few of them demonstrate glomerular endotheliosis, but many have evidence for underlying renal disease or preexisting hypertension that was not previously recognized (Table 4). Thus, preeclampsia is a difficult disease to diagnose.

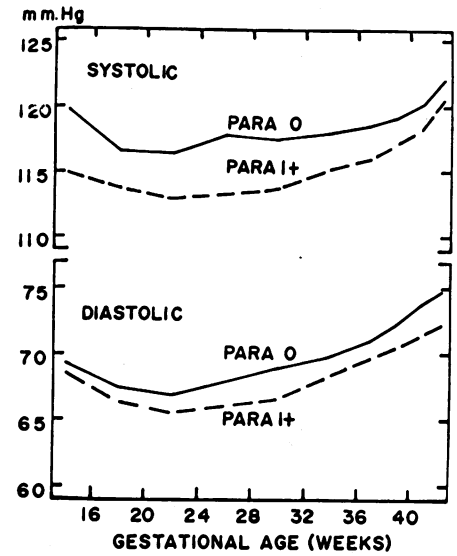

Figure 4.—Blood pressure during pregnancy: Mean blood pressure by gestational age of 6,662 white women who delivered single infants alive at term. (From Christianson.[12])

It is possible that the increased incidence of hypertension in later life in women who have had preeclampsia is due to inaccurate diagnosis. It is also possible, however, that a number of these women might not have become hypertensive had they not had preeclampsia. These possibilities have been successfully investigated in a study carried out by Leon Chesley.[13] This masterful study will probably never be repeated. He has followed a group of approximately 200 women who had eclampia in their first pregnancy. He chose eclamptic patients because he reasoned that if they were eclamptic and had seizures, they certainly had preeclampsia. They might have had other underlying diseases as well, but at least he

TABLE 4.—*Renal Biopsy Diagnoses of Patients With Clinical Diagnosis of Preeclampsia**

	Percent
Primigravida (62 patients)	
"Toxemic lesion"	70
Normal histology	5
Chronic renal disease (chronic GTN, chronic pyelonephritis)	25
Multigravida (152 patients)	
"Toxemic lesion" (with or without nephrosclerosis	14
Arteriolar nephrosclerosis	12
Normal histology	53
Chronic renal disease (chronic GTN, chronic pyelonephritis)	21

GTN = glomerulotubulonephritis

*Adapted from McCartney.[4]

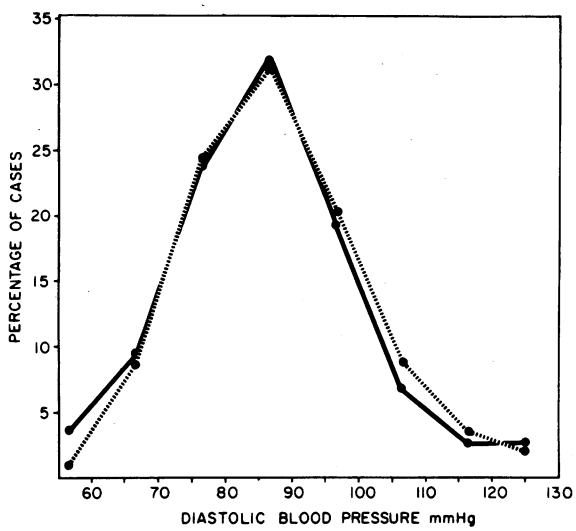

Figure 5.—Distribution of blood pressures in later life of primiparous women who had had eclampsia: Blood pressure distribution of 206 women who had had eclampsia in their first pregnancy (•—•), an average of 25 years after that pregnancy compared with 2,445 women matched for age and race from the Framingham study (•----•). (From Chesley et al.[13])

could be sure he was not dealing with women whose usually elevated blood pressure had become evident once again in late pregnancy. He followed these women for 42 years; two patients were lost to follow-up (Figure 5). I present the 25-year follow-up because at 25 years, women from the Framingham study could be an appropriate control group; however, beyond 25 years Chesley no longer had valid control groups for these elderly women. Comparing blood pressure distribution in the formerly eclamptic women with that of the controls shows that the distributions were identical. No matter how hypertension was defined, the incidence of hypertension was not increased in women who had been eclamptic during their first pregnancy, indicating that the eclampsia did not cause damage that led to hypertension in later life. Those women who became hypertensive were already destined to become so.

Let us use this information to attempt to formulate a philosophy of management. The most appropriate management would, of course, be to prevent the condition. This is not possible at present because we do not know what causes the disease. We do know the condition is more common among women of lower socioeconomic classes. Attempts have been made to link nutrition or vitamins to preeclampsia. Pregnant women have been starved, had their salt intake restricted or increased, fed high (or low) carbohydrate or high protein diets.[14] None of these treatments has been successful in preventing preeclampsia. We are able, however, to prevent preeclampsia from developing into eclampsia. Because the termination of the disease occurs with the termination of pregnancy, this preventive approach is possible.

Thus, we are forced to adopt a philosophy of management that uses the little information we do have to approach the condition rationally. It is important to remember that the signs and symptoms of the disease—blood pressure elevation and sodium retention—are not causal abnormalities. Also, because delivery will prevent a preeclamptic woman from becoming eclamptic and maternal deaths from the condition are limited to women with eclampsia, we would have a very efficient form of therapy if all we were considering was maternal well-being. However, for a woman with mild preeclampsia and a baby ten weeks before term, it is not always appropriate treatment for the fetus. I emphasize this because when considering advances in therapy, we must use as the indicator of successful therapy, not blood pressure changes or the effects on sodium retention, but the effect of the treatment on fetal well-being. If we use pharmacological agents or dietary manipulations to manage preeclampsia, the end point of successful therapy must be improved perinatal survival. Unfortunately, attempts to manage the disease pharmacologically—whether the pharmacological approach is something as irrational as diuresis in a woman whose plasma volume is already depleted, or whether it is lowering blood pressure because this is something we can measure, or even if it is therapy that seems rationally based on an attempt to increase blood flow to a number of important organs—have never improved fetal survival. I think the explanation is that the condition is present long before we make the clinical diagnosis and that there are probably already irreversible changes by this time. Thus, appropriate therapy might increase uterine blood flow, but there could already be vascular changes that prevent the increased uterine blood flow from being translated into increased placental perfusion.

The approach that obstetricians should take is to decide whether the fetus is at greater risk if left in utero or delivered. Fortunately, today there are tests that allow evaluation of the intrauterine fetus. These tests of biophysical functions, which evaluate fetal heart rate changes in response to fetal movement and uterine contraction, are fairly

reliable indicators of fetal well-being.[15] Analysis of amniotic fluid surfactant content also provides a reliable indicator of fetal lung maturation.[16] Because the major cause of death for premature infants is respiratory disease secondary to decreased surface-active material, this analysis permits determination of the risk of delivery to the infant. Using these tests, an obstetrician may rationally weigh the risk to the fetus in utero against the risk of prematurity. If delivery is elected, it is important to realize that it will terminate the disease but not abruptly. In the case presented here, congestive heart failure developed and the woman was still hypertensive 48 hours post partum. Delivery institutes the resolution of the disease but does not abruptly cure it. Also, the medical condition must be managed in a way that allows delivery without putting the woman at increased risk.

The two major objectives of therapy are prevention of convulsions and, in an occasional patient, the lowering of blood pressure. The prevention of convulsions requires the prophylactic use of an anticonvulsant agent for women who are severely preeclamptic or who have had seizures. It is also used for women with mild preeclampsia because the condition is more likely to accelerate during labor than at any other time. The anticonvulsant agent that is usually used is magnesium sulfate. This drug has not been chosen because it has dramatic effects on uterine blood flow, or has specific hypotensive effects in the doses used, or is the most effective anticonvulsant agent, or the most specific against eclamptic convulsions. Rather, it is used because when given in therapeutic doses, its impact on the fetus is less than that of the other agents that have been used in the past. This has been demonstrated by the work of Pritchard and Pritchard,[17] who treated eclampsia with magnesium sulfate in pregnancies involving 122 fetuses (Table 5). Among the fetuses that weighed more than 1,800 grams at the time eclampsia was diagnosed, there were no perinatal deaths. This is the standard against which all other approaches to anticonvulsant therapy during pregnancy must be judged.

When I first moved from internal medicine to obstetrics, I was appalled at using a drug—magnesium sulfate—that I had only known previously as a cathartic or an agent for animal euthanasia in the physiology laboratory. However, based on the considerations presented, it is a rational approach to therapy and safe when used appropriately. It is, however, a potentially lethal drug, the most serious problems being cardiac arrest and respiratory paralysis (Table 6).[18] These occur at serum concentrations above therapeutic levels. Empiric dosage schedules have been developed[3] that use either intramuscular or intravenous therapy or a combination of both. The initial dose recommended in these schedules is safe in all women regardless of renal function because the initially administered magnesium is diluted by distribution.[19] However, once the woman has received the initial dose of this drug, it is important to pay attention to urinary output because magnesium is excreted solely by the kidney. In women with adequate urinary output, the empiric approaches are safe and the levels of magnesium are judged grossly by following deep tendon reflexes. Deep tendon reflexes are lost at 10 mEq per liter, and the toxic effects occur above about 15 mEq per liter. A woman who has not lost deep tendon reflexes and has adequate urine output can safely continue to receive magnesium by the empiric dosage schedules. However, if urine output is less than 40 ml per hour or deep tendon reflexes are absent, therapy must be guided by measuring serum magnesium levels.

While anticonvulsant prophylaxis is used in all patients, only occasional patients will require antihypertensive therapy. Certainly, it would be diffi-

TABLE 5.—*Eclampsia: Fate of Fetuses Weighing 1,000 Grams or More at Parkland Memorial Hospital, 1955-1975**

	No. of Fetuses
Total in study	122
Dead when eclampsia diagnosed	7
Alive when eclampsia diagnosed	115
Intrapartum death	1†
Born alive	114
Neonatal deaths	4‡
Survived	110

*Adapted from Pritchard and Pritchard.[17]

†Fetus weighing 1,200 grams.

‡All weighed less than 1,800 grams; all 100 fetuses weighing 1,800 grams (4 pounds) or more and alive when eclampsia diagnosed survived.

TABLE 6.—*Effects of Magnesium Sulfate Given in Increasing Doses*

Effects	*Dose (mEq/liter)*
Therapeutic level	4-6
Electrocardiographic changes	5-10
Loss of deep tendon reflexes	10
Respiratory paralysis	15
General anesthesia	15
Cardiac arrest	>25

cult to argue that before our patient went into congestive failure, lowering her blood pressure was an important part of management. We use antihypertensive agents when blood pressure elevation is to a degree that increases the risk of intracranial bleeding. Antihypertensive therapy is used in women with diastolic pressures that are consistently greater than 110 mm of mercury. An agent must be chosen that will rapidly lower blood pressure, given the special considerations of safety of the fetus (Table 7). Trimethaphan is not used because it decreases cardiac output and uterine blood flow. Also, pregnant women are exquisitely sensitive to ganglionic blockers. Studies using animals indicate that sodium nitroprusside presents the same problem to the fetus as has been reported for adults receiving the drug; that is, with large doses given over a long time, serum thiocyanate concentrations increase. Diazoxide has been used extensively in pregnancy. However, we choose not to use it for the following reasons: (1) least important, it has effects on fetal carbohydrate metabolism; (2) if blood pressure of pregnant animals is lowered with diazoxide, uterine blood flow decreases and (3) most important, it works too well. If blood pressure is lowered too much with diazoxide, the drug is present for a number of hours; during that time uterine blood flow is decreased with no good way to increase uterine perfusion. The antihypertensive drug that we choose to use is hydralazine, administered intravenously. The choice of hydralazine is not based on the fact that it is very good for uterine blood flow of pregnant hypertensive sheep, but primarily because it is not nearly as potent an agent as diazoxide, and "overshoot" is very unlikely. The goal of antihypertensive therapy in these acute cases is not to lower the blood pressure to its usual levels but rather to a level that will reduce the likelihood of intracranial bleeding. For this goal hydralazine is very effective. Because the maximal effect of the drug is about 20 minutes after administration and the duration of action is three to eight hours, a continuous intravenous infusion does not seem reasonable. Therefore, we administer the drug intravenously as a 5-mg bolus and repeat this every 20 minutes as necessary to lower diastolic blood pressure to between 90 and 95 mm of mercury.

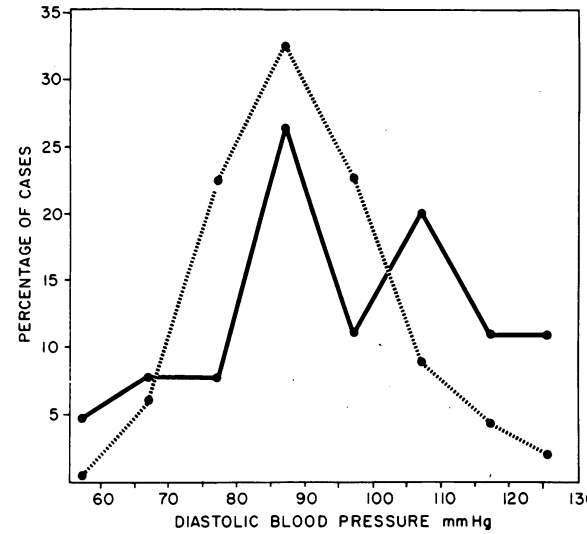

Figure 6.—Distribution of blood pressures in later life of multiparous women who had had eclampsia: Blood pressure distribution of 64 women who had had eclampsia in a pregnancy other than their first pregnancy (•—•), an average of 25 years after that pregnancy compared with 2,445 women matched for age and race from the Framingham study (•----•). (From Chesley et al.[13])

The last point I will consider is follow-up. We discussed the difficulty of diagnosing preeclampsia and that many of the women termed preeclamptic have evidence of another disease when renal biopsy specimens are studied. A woman who has preeclampsia in any pregnancy other than the first is clearly at risk of hypertension in later years (Figure 6). Chesley also followed women who were eclamptic in other than their first pregnancy.[13] There was an excess number of them with elevated blood pressures compared with the control women.

TABLE 7.—*Drugs for Treatment of Hypertensive Emergencies*

	Time Course of Action			*Dosage*			
Drug	*Onset (min)*	*Max. (min)*	*Duration (hr)*	*Intramuscular (mg)*	*Intravenous (mg)*	*Interval (hr)*	*Mechanism of Action*
Hydralazine	10-20	20-40	3-8	10-50	10-50	3-6	Direct dilation of arterioles
Diazoxide	1-2	2-3	4-12	..	300	3-10	Direct dilation of arterioles
	(min)	*(min)*	*(min)*	*Intravenous Solution (grams/l)*	*Intravenous Infusion Rate (mg/min)*		
Trimethaphan	1-2	2-5	10	2	1-15		Ganglionic blockade

Such patients deserve careful follow-up; however, one should keep in mind the fact that the blood pressure changes of preeclampsia do not resolve immediately. Many of the women normotensive at long-term follow-up in Chesley's study had still been hypertensive six weeks post partum. We usually reserve extensive evaluation for any woman who remains hypertensive three months post partum.

Conclusion

Preeclampsia-eclampsia is a fascinating disease. We do not know why it occurs. It changes a number of the physiological functions in ways that are dangerous to both the mother and her baby. We have been unsuccessful in attempting to improve fetal survival pharmacologically, probably because we start treatment after irreversible changes have occurred. At present, management remains a decision of whether the fetus is safest delivered or undelivered. Future progress in management of the disease should involve understanding what causes preeclampsia and developing simple tests that will allow us to recognize the disease before the clinical manifestations are present and before irreversible changes have occurred.

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